REMARKS

I. Informati n Disclosure Statement

Attached to the Office Action was a Form PTO-1449 showing that the Examiner considered the prior art cited in an Information Disclosure Statement ("IDS") submitted by Applicants on December 11, 2001. Applicants wish to bring the Examiner's attention to the supplemental IDS filed December 28, 2001. Upon issuance of the next communication from the Office, the Examiner is requested to complete and return the completed Form PTO-1449 showing that the Examiner considered the document cited in the supplemental IDS.

II. The Claimed Invention

The claimed invention is directed to an oral dosage form having a core material comprising omeprazole, an alkaline salt thereof, S-omeprazole or an alkaline salt thereof (hereinafter collectively referred to as "omeprazole"). Omeprazole is an acid labile substance susceptible to degradation and transformation in acidic and neutral media. Pursuant to pharmaceutical practice, an enteric coat is applied to dosage forms of drugs to protect the active ingredient from contact with acidic gastric juice. The protection afforded by the enteric coating layer is necessary to ensure that the active ingredient is transferred in an intact form to that part of the gastrointestinal tract where the pH is near neutral and where rapid absorption can occur. There are numerous publications describing enteric coated formulations comprising omeprazole or other proton pump inhibitors.

Therefore, it was indeed unexpected that an oral dosage form comprising omeprazole could be prepared without an enteric coating. In accordance with the claimed invention, the omeprazole core also includes one or more alkaline additives, one or more swelling agents and,

optionally, pharmaceutically acceptable excipients. The core material is coated with a disruptable, semi-permeable membrane comprising a water-insoluble polymer and a modifying agent to produce a delayed release of the active ingredient. Advantageously, the disruptable, semi-permeable membrane provides a delayed release of the active ingredient. As shown by Example 4 of the application, the claimed invention has the following rate of delayed dissolution:

TIME (hours) (after 2 hours of pre-exposure in acid medium)	% release of active ingredient
0.5	3
1	18
2	60
3	73

III. Claim Rejection – 35 U.S.C. §103(a)

Claims 1, 3-20 and 23-26 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Makino et al. (EP 0237 200) ("Makino").

Makino is directed to a pharmaceutical composition comprising a benzimidazole compound as the active ingredient. Makino discloses that the stability of the composition is improved by including a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium to the core material. The composition may also include additives, e.g., the additives disclosed on page 8, lines 14-20. The resulting mixture can be formulated into oral dosage forms such as tablets, capsules, powders and fine granules, by per se known means. In accordance with Makino, the dosage form may be coated by a per se known method for any of the following

purposes:

(a) taste making;
(b) providing an enteric coating; and
(c) providing a sustained release (See p. 8, lines 36-37).

For purposes (a)-(c), above, Makino provides a generic list of examples of coating agents without any disclosure or direction with respect to the suitability of any of the coating agents for a specific application (See p.8, lines 37-41). ***The coating agents include both water soluble and water-insoluble polymers.*** For example, hydroxypropylmethylcellulose and hydroxypropylcellulose are known water soluble polymers used to coat pharmaceutical dosage forms. In contrast, the claimed invention expressly requires a disruptable, semi-permeable membrane comprising a water-insoluble polymer, e.g., ethylcellulose, to obtain the claimed dosage form having no enteric coating.

Makino is silent on the possibility of preparing an omeprazole dosage form without an enteric coating. Therefore, Applicants respectfully submit that the only way that the Examiner could have isolated ethylcellulose from the generic disclosure of water soluble and water insoluble coating agents disclosed by Makino is with the benefit of impermissible hindsight. But for the subject application, it is not possible to glean a meaningful suggestion from Makino that a disruptable, semi-permeable membrane comprising a water insoluble polymer and a modifying agent could be used to prepare a dosage form of omeprazole having no enteric coating.

Applicants' position is supported by the Examples of Makino which are directed to the preparation of a dosage form and the application of an enteric coating. Examples 1-6 and 8 relate to the preparation of a dosage form, i.e., a granule. In accordance with Examples 7 and 9, the granule of Example 3 and 8, respectively, are layered with an enteric coating. Moreover, claim 9 of Makino is expressly directed to an enteric coated pharmaceutical composition.

Furthermore, there is no recognition by Makino that the formulation of the claimed dosage form, by virtue of the disruptable, semi-permeable membrane, would provide a ***delayed release*** of the active ingredient. As demonstrated by Example 4 of the application, the onset or start of dissolution is delayed and almost 3 hours are required to obtain a release of at least 73% of the active ingredient from dosage forms prepared in accordance with the claimed invention:

TIME (hours) (after 2 hours of pre-exposure in acid medium)	% release of active ingredient
0.5	3
1	18
2	60
3	73

In contrast, Makino states that dosage forms may be coated with a water soluble or water insoluble polymer by a per se method for the purpose of masking the taste or providing the dosage forms with enteric or sustained release property (page, 8, lines 36-37). Applicants submit that the pharmacological characteristics of a sustained release formulation is distinguishable from the delayed release of the claimed dosage form. A sustained release is a type of controlled release that provides a dissolution of the active ingredient over a sustained or extended period of time. However, such a sustained release is not characterized by the delayed or extended onset or start of dissolution which is observed with the claimed dosage form having a disruptable, semi-permeable membrane as shown by Example 4.

It is submitted, therefore, that Makino lacks any recognition of the possibility of either preparing a dosage form of omeprazole having no enteric coating or the requirements for preparing such a formulation. When viewed in its entirety, the disclosure of Makino is directed

to the preparation of enteric dosage forms of omeprazole which, at the time the claimed invention was made, were validated and widely accepted by the pharmaceutical industry. The cited prior art offers no suggestion of using a disruptable, semi-permeable membrane comprising a water insoluble polymer and a modifying agent to prepare an enteric-coatingless dosage form of omeprazole. Accordingly, the Examiner's analysis of Makino constitutes an improper hindsight reconstruction of the claimed invention.

For all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness. Withdrawal of the rejection based on Makino is requested.

IV. Claim Rejection – 35 U.S.C. §103(a)

Claims 1, 3-20 and 23-26 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over US 5,846,562 to Yanai et al. ("Yanai") and US 5,817,338 to Bergstrand et al. ("Bergstrand").

Yanai is directed to the preparation of an oral composition comprising a fumagillol derivative and, optionally, a proton pump inhibitor, e.g., omeprazole. As disclosed by Yanai, the drug-containing core may either be non-coated or enteric coated with a protecting layer separating the core from the enteric coating. (col. 14, lines 66-67). The protecting agents include hydrophilic substances such as a polysaccharide having a sulfate group, hydroxyalkyl group or carboxyalkyl group. ***The preferred protecting agent is hydroxypropylmethyl cellulose – a water soluble polymer.*** (col. 15, lines 1-6).

Applicants submit, therefore, that the primary reference to Yanai represents a teaching against the claimed invention. As recited in claim 1, the only independent claim, the core material is coated with a semi-permeable membrane comprising a water-insoluble polymer and a

modifying agent. Therefore, Yanai does not suggest the claimed invention having a disruptable, semi-permeable membrane to provide a delayed release of the active ingredient. Moreover, the deficiency of Yanai to suggest the claimed invention is not removed by the combination with Bergstrand which is cited by the Examiner for the alleged disclosure by Bergstrand of including an anti-tacking agent in the membrane layer.

Accordingly, whether taken alone or in combination, neither Yanai nor Bergstrand suggests the use of a semi-permeable membrane comprising a water insoluble polymer and a modifying agent to prepare the claimed enteric-coatingless dosage form of omeprazole. For all of the foregoing reasons, a *prima facie* case of obviousness has not been established. Withdrawal of the rejection based on the combination of Yanai and Bergstrand is request ed.

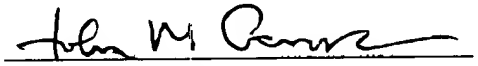
CONCLUSION

Applicants have made a good faith attempt to respond to the Office Action. It is respectfully submitted that claims 1, 3-20 and 23-26 are in condition for allowance, which action is earnestly solicited.

Any fee due in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: June 10, 2002

Respectfully submitted,



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